European Journal of Cardio-Thoracic Surgery 49 (2016) 1025–1027
doi:10.1093/ejcts/ezw040

Cite this article as: Rocco G, Nason K, Brunelli A, Varela G, Waddell T, Jones DR. Management of stage IIIA (N2) non-small-cell lung cancer: a transatlantic perspective. Eur J Cardiothorac Surg 2016;49:1025–7.

Management of stage IIIA (N2) non-small-cell lung cancer: a transatlantic perspective[†]

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Keywords: Non-small-cell lung cancer • N2 disease • Staging • Treatment

The selection of patients for surgical intervention in the setting of N2 nodal disease remains controversial with differences between centres, regions and continents. In an effort to highlight the similarities and differences in practices, we examined the staging and treatment of stage IIIA (N2) non-small-cell lung cancer (NSCLC) in North America and Europe.

DIAGNOSIS OF N2 DISEASE

The current guidelines in North America and Europe for the evaluation of mediastinal lymph nodes in the setting of lung cancer include endobronchial ultrasonography (EBUS) with fine-needle aspiration and cytological evaluation where lymph nodes are noted to be enlarged on computed tomography (CT; short axis ≥1 cm) or are avid on positron emission tomography (PET). Additional criteria for routine evaluation include central tumours, evidence of clinical N1 disease by imaging or tumours larger than 3 cm. The current recommendations are to proceed with video-assisted mediastinoscopy if the result of endosonographic evaluation is negative. Preresection invasive staging of the mediastinum is not necessary when there is an absence of enlarged lymph N1 and N2 nodes in tumours 3 cm or smaller in the outer third of the lung [1, 2].

These recommendations represent a departure from the guidelines published in 2007, which recommended mediastinoscopy for all patients with negative mediastinal imaging results, except for those with very small (T1) squamous cell cancers or clinical stage I NSCLC with negative mediastinal PET images [3, 4]. Both European and US guidelines recommend invasive staging for PET-positive mediastinal nodes, hilar N1 disease and central tumours. Despite PET-negative mediastinal lymph nodes, the European guidelines also suggest invasive staging for central tumours, evidence of clinical N1 disease by imaging or tumours larger than 3 cm. In contrast to the US guidelines, the European guidelines support invasive staging for PET-negative mediastinal lymph nodes 1.6 cm or larger on CT scan, even in the setting of peripheral clinical stage I disease [3, 4]. With these recommendations, the rate of unanticipated N2 disease is estimated to be below 10% [3].

With the current and previous guidelines in mind, a recent analysis examining variations in pulmonary resection practices between the USA and Europe sought to examine clinical practice with regard to surgical intervention in the setting of N2 disease. The Society of Thoracic Surgeons (STS) and the European Society of Thoracic Surgeons (ESTS) collaborated to share information and to develop commonly agreed-upon definitions for lung cancer staging, adverse events and related variables [5]. An unpublished analysis of this combined database included 78 212 lung resections (58% STS and 42% ESTS) between May 2010 and June 2013 and provided a robust comparison for the examination of practice variations. The difference in the incidence of N2 disease at the time of lung resection between the USA and Europe was striking. Despite similar distributions of T stage, only 8 and 16% of patients were found to have N2 disease after lobectomy and pneumonectomy, respectively, in the STS database, compared with 14 and 30% in the European registry.

This suggests that despite similarities in the published guidelines, there may be underlying differences between surgeons in the USA and Europe with regard to the aggressiveness of preoperative and intraoperative N2 nodal assessment. For example, surgeons in the USA may be more likely to use EBUS or mediastinoscopy to evaluate mediastinal nodes before planned resection, or they may perform more extensive biopsies of the nodes during the procedures, as opposed to relying on radiographic imaging. In essence, North American surgeons identify N2 nodes before resection, whereas European surgeons often identify them at the time of planned resection. Another consideration to account for the difference in N2 discovery at the time of operation between continents is that in most centres in the USA, biopsy-proven N2

[†]The article has been co-published with permission in *The Annals of Thoracic Surgery*, *European Journal of Cardio-Thoracic Surgery* and *The Journal of Thoracic and Cardiovascular Surgery*.

disease precludes immediate operative intervention, with the patient receiving either definitive chemoradiation or induction therapy. In comparison, in Europe, in single-station, non-bulky N2 disease, there is an increasing tendency to proceed directly to operation without induction therapy.

Although the rate of induction chemotherapy alone was similar between the two databases (7–8% before lobectomy), the proportion of patients who underwent induction radiotherapy before lobectomy was much higher in the STS database (7 vs 2%). Also, there may be differences in the intraoperative mediastinal lymphadenectomy performed at the time of lung resection, with the higher rate of N2 disease in European patients reflecting a more aggressive intraoperative N2 nodal assessment.

An important limitation of the two databases is the lack of information regarding long-term survival or cancer recurrence. In addition, details regarding the use of invasive staging modalities were not available in the two databases at the time of the analysis. These data are now being collected for the patients in the STS database and will be available for future analyses. Finally, both registries are voluntary and, unfortunately, still collect a minority (i.e. <10% in the STS database) of all patients undergoing surgical procedures for lung cancer. Therefore, whereas these findings must be interpreted with caution, more in-depth exploratory analyses are clearly warranted. Future studies from both the USA and Europe should include details about adherence to staging guidelines; this will allow a more comprehensive analysis of the differences in the prevalence of N2 disease at the time of lung resection.

SINGLE-STATION VERSUS MULTIPLE-STATION N2 DISEASE

The issue of 'how much' N2 disease continues to be a consideration in the recommendation of a therapeutic approach. In a recent study from Obiols *et al.* [6] of unsuspected N2 disease after mediastinal staging according to the ESTS guidelines, 406 of 540 patients underwent surgical exploration of the mediastinum before resection, whereas the remaining 134 directly underwent operation. After surgical staging of the mediastinum, unsuspected N2 disease was identified in 9% of patients, of whom 80% had single-station N2 disease and 90% of these received adjuvant chemotherapy or chemoradiotherapy. Importantly, the 3- and 5-year survivals for these patients with unsuspected N2 disease were 80 and 40%, respectively [6]. Legras *et al.* [7], from France, emphasized the importance of coexisting N1 disease or disease with multiple-station nodal involvement as independent prognosticators in patients with N2 disease. In a retrospective analysis of 871 patients with pN2 disease who underwent resection during a 20-year period, the 5-year overall survival rate was 25% for patients with pN2 disease; however, for patients with 'pure' single-station pN2 disease (i.e. no N1 or other N2 station disease), survival increased to 34% (hazard ratio [HR] = 1.64) [7]. Conversely, the presence of single-station N2 disease and concomitant N1 positivity (pN2N1) was associated with reduced survival (21%; HR = 2.09) [7].

The issue of single-station versus multiple-station N2 disease as separate prognosticators has been addressed in the recent literature [8]. Cho *et al.* [8] reviewed 196 patients who underwent resection for clinical N0/N1 disease and were found to harbour unsuspected pN2 disease; of those, 131 (67%) had single-station pN2 disease. The difference in 5-year survival was striking: 67% for single-station vs 36% for multiple-station pN2 disease [8]. In a study from Greece, single-station N2 disease was validated by multivariable analysis as the only favourable prognosticator of 3-year survival (odds ratio = 0.57) [9]. Funakoshi *et al.* [10] published an analysis of 141 patients with resected pN2 disease, 73% of whom had adenocarcinoma. Multistation pN2 disease was confirmed to be an adverse prognosticator; in fact, the 5-year survival rate was 58% for patients with unsuspected single-station pN2 disease, 50% for patients with concurrent clinical and pathological N2 disease and 24% for patients with unsuspected multistation pN2 disease [10]. One concern about these respective analyses is that the incidence of unsuspected multistation N2 disease is too high. With contemporary imaging and invasive mediastinal staging modalities, the incidence of unsuspected multistation N2 disease should be lower.

N2 SEEN FROM DIFFERENT ANGLES

Boffa *et al.* [11] explored the National Cancer Database to identify survival differences between induction and adjuvant chemotherapy administered in the setting of complete surgical resection in clinical stage III (N2) NSCLC in the USA. Overall, 2573 patients with cN2 were analysed; of those, 1217 patients (47%) were treated initially with an operation and 698 (57%) were confirmed to have pN2 disease [11]. Not surprisingly, patients with resected pN2 disease who underwent adjuvant chemotherapy had better 5-year survival than did those who underwent operation alone. No difference was observed between induction and adjuvant chemotherapy. Although the study could not fully control for the incidence of 'surprise N2' disease in the denominator, adjuvant chemotherapy did compare favourably with historical studies that established induction chemotherapy as standard [11].

Unpublished data from the 2015 report ('Silver Book') of the ESTS demonstrate that of 12 353 major anatomical resections performed after induction chemotherapy or chemoradiotherapy, 7918 (64%) had a well-specified p stage. Of those, 398 (5%) were staged as pNX, 4438 (56%) as pN0, 1335 (17%) as pN1, 1707 (21%) as pN2 and 40 (1%) as pN3. Conversely, of 27 700 anatomical resections performed in patients who had not previously received neoadjuvant treatment, 4248 (15%) were staged as pN1 and 3558 (13%) were staged as pN2. Interestingly, of 2298 patients with mediastinal nodes larger than 1 cm in the short axis on chest CT or with ^{18}F-fluorodeoxyglucose (FDG) avidity who did not undergo any induction treatment, 1621 (71%) actually had pN2 disease. However, in 2356 patients with cN2 disease, 935 (40%) received no invasive mediastinal staging (e.g. EBUS and mediastinoscopy) before operation. These data when contrasted with data from administrative databases in the USA suggest that, in Europe, surgical staging of the mediastinum, even with enlarged or FDG-avid N2 nodes, is performed less commonly and that primary operations for N2 disease occur more commonly.

Support for upfront surgical treatment comes from the group from Leicester, UK, who suggest that intentional resection of preoperatively known single-station N2 disease results in similar survival between patients with negative N1 and N2 PET–CT scans, but are found to have unsuspected pN2 disease at the time of operation [12]. In that study, the need for pneumonectomy, noncompliance with adjuvant treatment and multistation N2 nodal disease were adverse prognostic factors [12]. The study was limited by its retrospective nature, small sample size (30 patients with cN2 disease/1131 total patients [3%]) and failure to follow an

established mediastinal surgical staging protocol like that suggested by the ESTS [1].

In contrast, a Cardiothoracic Surgery Network survey revealed that only 12% of thoracic surgeons in the USA believe that surgical treatment should be the initial treatment modality for N2 disease [13]. The majority (84%) of respondents favour surgical treatment after induction therapy for microscopic single-station N2 disease, whereas 62% favour operation after induction therapy with bulky single-station N2 disease [13]. In North America, surgical treatment for cN2 disease is generally reserved after induction therapy, given these considerations: (i) patients with N2 disease are more likely to experience systemic failure; (ii) patients are more likely to receive full-dose and full-cycle chemotherapy when those are given preoperatively relative to adjuvant delivery and (iii) induction chemotherapy provides an assessment of tumour biology and treatment response. This approach is supported by the National Comprehensive Cancer Center guidelines and by other groups [14–16].

It is important to note that no study has shown superiority of chemotherapy/radiation (excluding surgical treatment as part of the multimodality management) when survival is the primary outcome [17]. Furthermore, in trials of NSCLC with N2 disease, patients who underwent operations as part of a trimodality treatment had improved overall survival compared with those who received chemoradiotherapy alone. A recent meta-analysis and an editorial from Europe suggest that in patients with PET–CT-positive ipsilateral, non-bulky N2 disease, surgical staging of the mediastinum should be eliminated and upfront operations performed, followed by adjuvant chemotherapy [17, 18]. There are no prospective trials to support this approach, and in the USA (where induction therapy is favoured for any N2 disease) this may be challenging; nonetheless, this is an interesting and potential clinical trial–provoking observation.

CONCLUSIONS

There are several similarities, but also selected differences, in the management of N2 NSCLC between thoracic surgeons in Europe and North America. In general, North American surgeons are more likely to surgically stage the mediastinum before operation, are less likely to offer surgical treatment when N2 disease is identified preoperatively and are more likely to use induction therapy before resection. In contrast, European surgeons may offer operation as the initial treatment followed by adjuvant therapy in selected cases of N2 disease, and they may perform a more aggressive intraoperative nodal dissection. Many issues remain unresolved regarding the role of operations in N2 disease, but all contemporary series support that surgical treatment should be part of the multimodality treatment of N2 disease. There are opportunities for European and North American thoracic surgeons and their teams to work across the Atlantic to construct adequately powered clinical trials to address these issues.

Funding

David R. Jones was supported in part by NIH/NCI Cancer Center Support Grant P30 CA008748.

Conflict of interest: none declared.

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